PB88-120720

Health and Environmental Effects Profile for Sodium Diethyldithiocarbamate

(U.S.) Environmental Protection Agency
Cincinnati, OH

Jan 84

U.S. Department of Commerce
National Technical Information Service
NTIS

EPA/600/X-84/136
January 1984

PB88-120720

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR SODIUM DIETHYLDITHIOCARBAMATE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO. EPA-600/X-84-136	2.
3. RECIPIENT'S ACCESSION NO. PB88 120720/AS	
4. TITLE AND SUBTITLE Health and Environmental Effects Profile for Sodium Diethyl Dithiocarbamate	5. REPORT DATE January 1984
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268	13. TYPE OF REPORT AND PERIOD COVERED
	14. SPONSORING AGENCY CODE EPA/600/22
15 SUPPLEMENTARY NOTES	

16. ABSTRACT The Health and Environmental Effects Profile for sodium diethyl dithiocarbamate was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Sodium diethyl dithiocarbamate has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for sodium diethyl dithiocarbamate is 2.5×10^{-1} (mg/kg bw/day)$^{-1}$ for oral exposure.

Quantitative estimates have been presented provided sufficient data are available. Sodium diethyl dithiocarbamate has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for sodium diethyl dithiocarbamate is 3.0×10^{-2} mg/kg bw/day for oral exposure.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT Public	19. SECURITY CLASS (This Report) Unclassified	21. NO. OF PAGES 40
	20. SECURITY CLASS (This page) Unclassified	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:
Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:
Bette Zwayer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

TABLE OF CONTENTS

		Page
1.	INTRODUCTION	1
	1.1. STRUCTURE AND CAS NUMBER	1
	1.2. PHYSICAL AND CHEMICAL PROPERTIES	1
	1.3. PRODUCTION DATA	2
	1.4. USE DATA	2
2.	ENVIRONMENTAL FATE AND TRANSPORT PROCESSES	4
	2.1. SOIL	4
	2.2. WATER	4
	2.3. AIR	5
3.	EXPOSURE	6
4.	PHARMACOKINETICS	7
	4.1. ABSORPTION	7
	4.2. DISTRIBUTION	7
	4.3. METABOLISM	7
	4.4. EXCRETION	8
5.	EFFECTS	9
	5.1. CARCINOGENICITY	9
	5.2. MUTAGENICITY	11
	5.3. TERATOGENICITY	11
	5.4. OTHER REPRODUCTIVE EFFECTS	11
	5.5. CHRONIC AND SUBCHRONIC TOXICITY	12
	5.6. OTHER RELEVANT INFORMATION	16
6.	AQUATIC TOXICITY	18
	6.1. ACUTE	18
	6.2. CHRONIC	18
	6.3. PLANT EFFECTS	18
	6.4. RESIDUE	19
	6.5. OTHER RELEVANT INFORMATION	19
7.	EXISTING GUIDELINES AND STANDARDS	20
	7.1. HUMAN	20
	7.2. AQUATIC	20
8.	RISK ASSESSMENT	21
9.	REFERENCES	23
	APPENDIX I: Literatature Searched	31
	APPENDIX II: Derivation of q^*_1	33

LIST OF ABBREVIATIONS

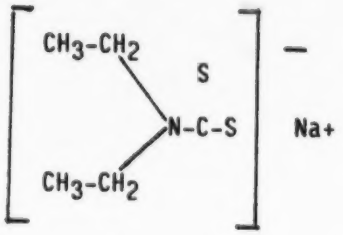
ADI	Acceptable daily intake
CEC	Cation Exchange Capacity
CNS	Central nervous system
DNA	Deoxyribonucleic acid
i.p.	Intraperitoneally
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
s.c.	Subcutaneous
TWA	Time-weighted average
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Sodium diethyldithiocarbamate is also known as: diethylcarbamodithioic acid, sodium salt; DEDC; diethyldithiocarbamate sodium; diethyldithiocarbamic acid, sodium salt; diethyl sodium dithiocarbamate; dithiocarb; sodium DEDT; and sodium salt of N,N-diethyldithiocarbamic acid [International Agency for Research on Cancer (IARC), 1976].

Chemical production in the United States was first reported in 1940 (IARC, 1976). The structure of sodium diethyldithiocarbamate (dithiocarb) is depicted below:



The molecular formula is $C_5H_{10}NNaS_2$, and the molecular weight is 171.3. The Chemical Abstract Service (CAS) Registry Number is 148-18-5.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Dithiocarb is available as a 25% aqueous solution of a pale yellow color (IARC, 1976).

Some of the physical and chemical properties are listed below (IARC, 1976):

Specific Gravity:	1.08-1.10
Melting Point:	94-96°C
Solubility:	freely soluble in water at 20°C; soluble in ethanol; decomposes in alkaline solution
UV absorption data:	λmax = 257 nm and 290 nm

1.3. PRODUCTION DATA

Dithiocarb is prepared by the addition of carbon disulfide to an aqueous solution of diethylamine and sodium hydroxide (IARC, 1976).

Dithiocarb was produced in small quantities by a number of companies in 1977 (Table 1-1).

Frederick Smith Chemicals, Brin-Mont Chemicals, Guardian Chemicals, Pennwalt and Hach Chemical Company are no longer listed as producers of dithiocarb: but Alco Standard of Chattanooga, TN, recently started its production [Stanford Research Corporation (SRI), 1983].

1.4. USE DATA

Dithiocarb is used as an accelerator in the rubber processing industry. This compound is also used in fungicide preparation; as a chelating agent; as an oxidation inhibitor, and as an analytical reagent (IARC, 1976).

TABLE 1-1

Producers and Estimated Production Volumes of Dithiocarb in 1977*

Producers/Location	Volume (lbs)
Kodak Rochester, NY	1000-10,000
Pennwalt Wyandotte, MI	NR
Frederick Smith Chem. Columbus, OH	NR
Frank Enterprises, Inc. Columbus, OH	1000-10,000
Hach Chem. Co. Ames, IA	under 1000
Brin-Mont Chemicals Greensboro, NC	10,000-100,000
Vanderbilt Chem. Corp. Bethel, CT	NR

*Source: U.S. EPA, 1977

NR = Not reported

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. SOIL

The fate and transport of dithiocarb in the soil is likely to be determined by its ability to undergo biological transformation and chemical reactions. Microbial degradation of dithiocarb is likely to occur slowly in the soil environment because of the inherent microbial toxicity of the dithiocarbamates (Kaufman, 1967). Dithiocarb can be converted in soils to diethylamine, a nitrosamine precursor, as demonstrated by Tate and Alexander (1974); however, the biodegradation half-life of this compound was not established. Dithiocarb may undergo hydrolysis in soils (Tate and Alexander, 1974), though no quantitative estimate of the rate of this reaction was made.

The two processes that control the transport of dithiocarb in the soil are volatilization and leaching. Judging from the ionic nature and relatively high water solubility of this compound, it is unlikely that dithiocarb will undergo substantial volatilization or leaching from soils with a high CEC. In contrast this compound may leach substantially from soils with a low CEC, because of its high solubility in water.

2.2. WATER

The fate of dithiocarb in the aqueous media depends on its ability to undergo chemical and photochemical reactions as well as microbial degradation. Dithiocarb was found to be stable in aqueous solution at pH 7 but decomposed under slightly acidic conditions (pH 5-6.7), producing carbon disulfide and a salt of diethylamine (Lopatecki and Newton, 1952). This compound was also reported to decompose in alkali solutions with liberation of CS_2 (Sandmeyer, 1981; Burkart et al., 1968). Since many waterbodies are slightly acidic or basic, hydrolysis may be significant in determining

the fate of this compound in aquatic media. Data regarding the significance of photochemical reactions of this compound were not located in the sources cited in Appendix I.

Degradation by microorganisms is likely to occur in the aquatic media, although no data specific to the natural environment were located in the literature searched. One study described the degradation of the dithiocarbamates in activated sludge and found >96% of the compounds were removed after 23 days (Brink, 1976). Although these data are of limited applicability in the natural environment, they do indicate that microorganisms may make a significant contribution to the removal of dithiocarbamates from aquatic media.

Pertinent data regarding the transport of dithiocarb in the aqueous media were not located in the available literature (see Appendix I); however, some inferences can be made from its physical properties. If chemical hydrolysis or microbial transformation does not occur, dithiocarb is likely to be dissolved and transported in water. If soil particles or sediment are present in the water, dithiocarb may adhere to suspended matter that has a high CEC and be transported in this way.

2.3. AIR

The fate and transport of dithiocarb in the atmosphere will depend on its ability to react with O_3, NO_x and free radicals, (e.g., RO•, O• and RO_2•), its ability to undergo phytolysis, and its capacity to adsorb to particulate matter. Chemical or photochemical reactions in the atmosphere were not located in the literature searched. Based, however, on its fate in soil and water, it is likely that the compound will undergo hydrolysis in moist air. Considering its high water solubility, the compound is likely to be removed from the atmosphere primarily by wet deposition.

3. EXPOSURE

No monitoring data for this compound were located in STORET or elsewhere.

4. PHARMACOKINETICS

4.1. ABSORPTION

Rats receiving levels of 500 mg of dithiocarb in 1-2 mℓ water/kg body weight by gavage reached plasma levels of 2 mg/ℓ dithiocarb in 3 hours (Baselt and Hanson, 1982). A half-life for absorption of 26 minutes was determined when ^{35}S-dithiocarb dissolved in 2M phosphate buffer was injected into the small intestinal lumen of adult male Wistar rats at a dose of 25 mg/kg (Craven et al., 1976). Administration of the same preparation by gavage resulted in a half-life for disappearance from the stomach of 39 minutes. Radioactivity was detected in the plasma at 11.3 µg/L (expressed as dithiocarb) by 15 minutes after administration (Craven et al., 1976).

4.2. DISTRIBUTION

Within 15 minutes of dosing rats with 25 mg (222 µmoles ^{35}S)/rat ^{35}S-dithiocarb i.p., nonprotein-bound radiolabel was detected in the plasma (1561 nmoles/mℓ plasma) and in the liver (3211 nmoles/g liver). A substantial amount (>45% within 15 minutes of dosing) of radioactivity also was found to be bound reversibly to soluble proteins of liver and plasma (Stromme, 1965).

4.3. METABOLISM

A small amount (<0.1%) of unchanged dithiocarb was detected in the urine of rats receiving i.p. injections of 25 mg ^{35}S-dithiocarb/rat. One hour after dosing, 96.1% of the radiolabeled urinary metabolites was of S-glucuronide conjugate and 3.9% inorganic sulfate. Within 1 hour after dosing, 7% of the administered ^{35}S was recovered as carbon disulfide in the expired air (Stromme, 1965).

4.4. EXCRETION

After receiving 25 mg ^{35}S-dithiocarb/rat i.p., rats expired 7% of the radiolabel as carbon disulfide within 1 hour and 10% within 4 hours. One hour after dosing, only 0.03% of the labeled urinary products were identified as unchanged dithiocarb; 96.1% was identified as S-glucuronide conjugate and 3.9% as inorganic sulfate. After 4 hours, 0.06% of the label was identified as dithiocarb, 76.3% as S-glucuronide conjugate and 23.6% as inorganic sulfate (Stromme, 1965). Following oral administration of 25 mg ^{35}S-dithiocarb/kg to rats, 60% of the administered radioactivity was excreted in urine and in the expiratory air within 3 hours; elimination was 96% complete by 72 hours. By 72 hours, about half of the administered radioactivity was expired as carbon disulfide; the remainder was excreted mainly in the urine with a small amount detected in the feces (Craven et al., 1976).

5. EFFECTS

5.1. CARCINOGENICITY

The potential carcinogenic effects of dithiocarb have been assessed in chronic and acute exposure studies (BRL, 1968; Lanes et al., 1969; NCI, 1979).

Male and female mice, strains B6C3F1 and B6AKF1, were gavaged with 215 mg dithiocarb/kg/day [the maximum tolerated dose (MTD), which was calculated using the average body weight of mice at the start of the study and not corrected for weight gain] from days 7-28 of age. Dithiocarb was then administered in the diet at a level of 692 ppm for about 18 months. Negative controls consisted of untreated and vehicle treated mice of both sexes of both strains. At 78 weeks of age, the mice were sacrificed and necropsied. Total tumor incidences for B6C3F1 mice were 10/17 treated males and 1/18 treated females versus 22/79 control males and 8/87 control females. Hepatomas were found in 7/17 treated males compared with 8/79 in control males. Pulmonary adenomas were found in 3/17 treated males and 5/79 control males. Reticulum cell sarcoma was present in 1/18 treated females versus 4/87 control females. For strain B6AKF1, total tumor incidences were 6/18 treated males, 2/18 treated females, 16/90 control males and 7/82 control females. No hepatomas were present in treated mice of this strain, but pulmonary adenomas were found in 5/18 and 1/18 treated males and females, respectively, compared with 9/90 and 3/82 control males and females, respectively. The incidence of reticulum cell sarcoma was 1/18 treated males, 1/18 treated females, 1/90 control males and 3/82 control females (BRL, 1968; Innes et al., 1969).

B6C3F1 and B6AKF1 mice (18/sex/strain) were given a one-time s.c. injection of 464 mg dithiocarb/kg in water on the 28th day of age and were

sacrificed 18 months later. For strain B6C3F1, 1/18 treated males had reticulum cell sarcoma and 1/18 treated males had pulmonary adenoma, compared with 8/141 and 4/141 control males for the two tumor types, respectively. For strain B6AKF1, 2/18 treated males had pulmonary adenomas compared with 6/161 control males. No tumors were found in female mice of either strain (BRL, 1968).

IARC (1976) found the results of these two studies insufficient to make a judgment regarding the carcinogenicity of dithiocarb. More recently, NCI (1979) conducted a bioassay of dithiocarb for carcinogenicity in rats and mice and obtained negative results. Dithiocarb was administered to groups of 50 F344 rats of each sex at 1250 or 2500 ppm in the diet for 104 weeks and to groups of 50 B6C3F1 mice of each sex at 500 or 4000 ppm in the diet for 108 or 109 weeks. Untreated controls consisted of 16 male rats, 20 female rats and 20 male and 20 female mice. For rats, no treatment-related effects on mortality were observed. Upon necropsy after the treatment period, gross examination and comprehensive histological examination revealed no significantly increased tumor incidence of any type in the treated rats as compared to controls. For mice, no treatment-related effects on mortality were observed. Alveolar/bronchial adenomas and carcinomas were seen in 7/49 treated female mice of the 500 ppm group and 8/50 treated females of the 4000 ppm group. Adenomas and carcinomas were not seen in control females. In males, the incidence of these tumor types was 14/50 for the low-dose group, 14/49 for the high-dose group and 6/19 for the control males. There were, however, no significant increase in any tumor types for either male or female mice. The investigators concluded that dithiocarb was not significantly carcinogenic to rats or mice under the conditions of the bioassay.

5.2. MUTAGENICITY

Only a few studies concerning the genotoxic potential of dithiocarb were located. Treatment of Vicia faba root tips with dithiocarb concentrations of 2.5×10^{-3}M for 3 hours or 5×10^{-3}M for 1 hour resulted in 6/100 or 11/100 abnormal metaphases, 6/100 or 14/100 isolocus chromosome breaks and 4/100 or 4/100 chromatid exchanges for the two respective concentrations of dithiocarb (Kihlman, 1957). The frequency of these aberrations among controls was 0.2/100 abnormal metaphases (500 metaphases analyzed), 0.2/100 isolocus chromosome breaks and 0/100 chromatid exchanges. Harman et al. (1970) fed male LAF1 mice a 1.0% (by weight) dithiocarb diet and observed a 75% frequency of chromosome aberrations in the regenerating liver cells of mice 72 hours after regeneration was induced by carbon tetrachloride administration. This was not a significant increase when compared with a frequency of 72.8% aberrations in controls. An abstract of a study by Ceruzzi (1974) reported that the effects of dithiocarb on Bacillus subtilis were the inhibition of development, induction of degenerate forms and the prevention of sporulation. Dithiocarb also inhibited ^{3}H-thymidine uptake into DNA-synthesizing human lymphocytes, stimulated by the mitogens phytohemagglutanin or concanavalin A in a dose-related fashion by about 10% at a concentration of 10^{-10}M, 33% at 2.5×10^{-10}M and 73% at 5×10^{-10}M (Neveu et al., 1980).

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of dithiocarb were not located in the available literature.

5.4. OTHER REPRODUCTIVE EFFECTS

Pregnant rabbits given dithiocarb intravenously in volumes of either 5 or 10 mℓ of a 0.1 g/mℓ solution 5 times/week from days 1-20 of pregnancy

failed to deliver litters. Pretreatment of pregnant rabbits with copper sulfate (copper levels were reduced by dithiocarb) failed to prevent fetal resorption (Howell, 1964). Sakai et al. (1979) found in dogs that ejaculation was suppressed, but not erection, within 1 hour of an i.p. injection of 50, 75 or 100 mg dithiocarb/kg. Partial recovery occurred after 3 hours with complete recovery by 24 hours. This suppression was associated with decreased levels of noradrenalin in the caudate, the epididymis and the posterior urethra, decreased serotonin levels in the posterior hypothalamus and increased levels of serotonin in the epididymis. Rice (1964) reported gross morphological alterations of the tails of human spermatozoa upon treatment with dithiocarb in vitro. The anomalies consisted of the formation of bead like crystals after a small amount of dithiocarb was dissolved in a drop of semen on a microscope slide. Mixing of dithiocarb at a concentration of 97.4 pmole/cell with human semen resulted in a 9.7% increase in the volume of spermatozoa (Brotherton, 1977).

5.5. CHRONIC AND SUBCHRONIC TOXICITY

The only available chronic toxicity study is the NCI (1979) oral carcinogenicity study, which provides limited information on systemic toxicity. Additional information can be obtained from a 90-day feeding study in rats and dogs by Sunderman et al. (1967), 4-7.5-month i.p. studies in lambs (Howell et al., 1970) and rabbits (Edington and Howell, 1966), and several oral and i.p. studies of shorter duration.

The experimental protocol for the NCI (1979) study has previously been described in Section 5.1. Dietary levels of 1250 or 2500 ppm dithiocarb had no effect on mortality (as compared with controls) in rats. Mean body weights of the high-dose male rats and of both low- and high-dose female rats were slightly lower than those of the corresponding controls throughout

the study. This effect was dose-related in the females. Information on food consumption was not provided in the report. Clinical signs or histopathologic evidence of systemic toxicity were not observed, however, cataracts of the eye were found in treated female rats. The incidence of cataracts was 0/20 control females, 14/50 low-dose females and 6/50 high-dose females. Only eyes that were grossly abnormal were examined microscopically and the NCI (1979) was therefore uncertain of the significance of this finding. Cataracts were not observed in male rats. Assuming that rats consume the equivalent of 5% of their body weight/day as food, dietary levels of 1250 and 2500 ppm dithiocarb would correspond to dosages of 62.5 and 125 mg/kg/day.

In the NCI (1979) carcinogenicity study, administration of 500 or 4000 ppm dithiocarb in the diet had no effect on the mortality of treated mice, as compared to controls mortality among the high-dose females, however, was somewhat lower than among control females. Mean body weights for both males and females receiving either dietary level of dithiocarb were lower than those of the corresponding controls and were dose-related throughout the study. Food consumption was not provided in the report. The histopathologic examinations included nonneoplastic lesions, but no such lesions were discussed under results; hence, it may be inferred that there were no notable nonneoplastic findings. Assuming that mice consume the equivalent of 13% of their body weight/day as food, dietary levels of 500 and 4000 ppm dithiocarb would correspond to dosages of 65 and 520 mg/kg/day.

Sunderman et al. (1967) administered dithiocarb to albino rats and beagle dogs orally at doses of 0, 30, 100 or 300 mg/kg daily for 90 days. Each group of rats consisted of 25 animals/sex; the groups of beagle dogs were composed of 2 males and 2 females each. For rats, the only treatment-

related differences observed were significantly decreased mean red blood cell counts and renal changes in the 300 mg/kg group. The renal tubule had granular cytoplasm, irregular dilatation, swelling and congested glomeruli. No changes were seen in the eyes, liver, gonads, skeleton, endocrine glands or gastrointestinal tract of treated rats as compared to controls. In the dogs receiving 300 mg dithiocarb/kg, one female died on day 70 of treatment. Terminal congestive changes in the livers were observed in some dogs. Some of the dogs treated at high dithiocarb levels had enteritis and colitis, and one 300 female from the 300 mg/kg group had erythroid hyperplasia of the bone marrow. Hematologic changes at the 300 mg/kg level included decreased mean values for cell-volume, hemoglobin concentrations and red blood cells. The three dogs surviving the 90-day treatment at 300 mg/kg continued receiving oral doses of dithiocarb; however, the dosage levels were raised to 500 mg/kg for 3 days, 600 mg/kg for the next 3 days, 1000 mg/kg for another 3 days and finally 2000 mg/kg until death ensued (1-7 days). As the dose increased, the physical condition of the dogs deteriorated with tremors, general weakness, anorexia, incoordination and ataxia resulting in to death (Sunderman et al., 1967).

Howell et al. (1970) treated five 2-day-old and eleven 1-month-old lambs of the Clun Forest or Clun Forest crossed strains with i.p. injections of dithiocarb in phosphate buffer at doses of 165 or 330 mg/kg 5 times/week for up to 16 weeks, when all but one treated lamb had died. Four 2-day old lambs served as vehicle controls. The surviving lambs were sacrificed and necropsied for histological effects on the CNS. Livers and thoracic spinal cords were analyzed for copper, but no correlations between copper levels and toxicity were made. Treated lambs were found to have local peritonitis. Following 3 weeks of treatment histological examination revealed eosino-

philic round or ovoid lesions in the medulla, Clarke's column and the spinal cord. These lesions became progressively worse with vacuolization as treatment continued. Treatment for at least 5 weeks resulted in swollen axons in the posterior thoracic and anterior lumbar segments of the spinal cord. No correlation between dose level and severity of lesions was mentioned in the study.

Ten Dutch male rabbits received 330 mg dithiocarb/kg by gavage 5 days/week for 4, 6 or 9 weeks, after which time they were sacrificed and necropsied. An additional 10 rabbits served as controls. Histological examination revealed lesions of Wallerian degeneration and eosinophilic bodies in the medulla and spinal cord becoming progressively worse with long exposures. In rabbits receiving dithiocarb for 9 weeks, significant decreases in nerve fiber diameters were seen when compared with control animals (Rasul and Howell, 1973). Similarly, daily i.p. administration of dithiocarb to 7 rabbits for up to 7.5 months produced signs of incoordination, swollen axons and ballooning of myelin sheaths (characteristic of early Wallerian degeneration) in the white matter of the spinal cord and in the sciatic nerve. Some early degenerative changes in the gray matter of the spinal cord were also produced (Edington and Howell, 1966). These lesions did not occur in saline-treated controls. Copper levels of the liver and spinal cord of treated rabbits were markedly increased over those of controls.

Iwata et al. (1970) administered 350 mg dithiocarb/kg twice daily by i.p. injection to male Sprague-Dawley rats for 2 weeks. Upon necropsy, it was determined that copper accumulated in the CNS significantly in the cerebral cortex ($P<0.05$), brain stem ($P<0.05$) spinal cord ($P<0.01$) and also in the liver ($P<0.01$) when compared with controls. No significant differences were seen in the cerebellum. Crossley et al. (1969) injected Sprague-

Dawley rats (route not specified) every 2 days for 9 weeks with 66.5 mg dithiocarb/kg in phosphate buffer. Mean body weights of treated rats were significantly lower than vehicle treated controls after 6 weeks of treatment. At 7 weeks, mean systolic blood pressure was reduced significantly.

5.6. OTHER RELEVANT INFORMATION

Dithiocarb has been studied extensively for its biological effects on a number of systems, for its ability as a metal chelating agent to treat symptoms of metal poisoning and for its potential in cancer chemotherapy. Some representative studies are listed below:

Effects on biochemical parameters and enzyme activities:

Dithiocarb reduced the noradrenaline and increased the dopamine contents of the ileum of rats and rabbits (Collins and West, 1968).

Rats injected i.p. with 400 mg dithiocarb had elevated dopamine-beta hydroxylase levels in the adrenals (Magos and Jarvis, 1981).

Dithiocarb inhibited blood serum leucine aminopeptidase activity *in vitro* (Maggiore et al., 1981).

Dithiocarb inhibited human plasma kininase and erythrocyte kininase activities *in vitro* (Vennerod, 1970).

Dithiocarb decreased the level of microsomal cytochrome P-450 and inhibited the activities of aniline hydroxylase, carboxylesterase and ethylmorphine N-demethylase in rats *in vivo* and *in vitro* (Zemaitis and Greene, 1979).

Effects on the CNS:

Dithiocarb caused increased uptake of copper and zinc in the brains of mice (Aaseth et al., 1979).

Dithiocarb inhibited monoamine oxidase activity, increased 5-HT levels and depressed noradrenaline levels in the CNS of rabbits (Edington, 1968).

Dithiocarb caused elevated brain dopamine levels in mice and rats (Maj and Vetulani, 1970).

Dithiocarb injected into the brains of mice caused hypothermia and CNS depression (Doggett and Spencer, 1973); dithiocarb injected into the brains of rats produced decreased brain noradrenaline levels, increased the dopamine levels and reduced locomotor activity (Kleinrok et al., 1970).

Use for treating metal poisoning:

Dithiocarb has been used effectively in nickel carbonyl poisoning (Sunderman et al., 1967) and has been studied for its efficacy for nickel carbonyl toxicity in rats (Baselt and Hanson, 1982).

Dithiocarb protected mice from cadmium toxicity (Gale et al., 1981).

The potential of dithiocarb as a chemotherapeutic agent in the treatment of human cancer has been studied with respect to its immunologic activity (Renoux and Renoux, 1981).

The LD_{50} values for various species and various routes of exposure as reported by NIOSH (1983) are:

rat - oral	- 1500 mg/kg
mouse - oral	- 1500 mg/kg
mouse (i.p.)	- 1500 mg/kg
rabbit (s.c.)	- 500 mg/kg

6. AQUATIC TOXICITY

6.1. ACUTE

The acute toxicity of dithiocarb was reported for the goldfish, Carassius auratus. Exposure to 1.25, 2.25 or 3.125 mg dithiocarb/ℓ for 1 hour resulted in no deaths or toxic effects (Danscher and Fjerdingstad, 1975). Exposure to 7.5 mg/ℓ for 1 hour was lethal within 24 hours post-exposure to ~12.6% (17/135) of the tested animals. Exposure to 15, 25 and 100 mg/ℓ dithiocarb for 1 hour resulted in 67% (8/12), 43% (13/30) and 100% (6/6) mortality, respectively. At a dose of 7.5 mg dithiocarb/ℓ, most fish were less active and had "characteristic folding together of fins" (Danscher and Fjerdingstad, 1975). Toxic symptoms occurred within 3 hours of exposure, and those fish surviving after 24 hours appeared to recuperate.

The acute toxicity of two dithiocarb formulations (each contained 80% dithiocarbamate) was studied in the crustacean, Gammarus pulex (Bluzat et al., 1982a). The 24, 48, 72 and 96-hour LC_{50} values for Product A (aqueous suspension) were 13.99, 1.21, 0.41 and 0.195, respectively. The 24, 48, 72 and 96-hour LC_{50} values for Product B (which contained adjuvants) were 4.77, 0.48, 0.2 and 0.13 mg/ℓ, respectively. The 48 and 96-hour LC_{50} values for Product A were 15 and 10 mg/ℓ, respectively, for the mollusk, Lymnaea stagnalis. Product B was more toxic with 48 and 96-hour LC_{50} values of 4 and 3 mg dithiocarb/ℓ, respectively (Bluzat et al., 1982b).

6.2. CHRONIC

Pertinent data regarding the chronic effects of dithiocarb on aquatic organisms were not located in the available literature.

6.3. PLANT EFFECTS

The effects of dithiocarb at 17.1 mg/ℓ for periods of 3, 5 or 6 days had little effect on the growth and flower production of the duckweed, Lemna

gibba. During 3 and 5-day exposure experiments, the yield of reproductive fronds was decreased, as compared with controls. The response exhibited by dithiocarb treatment in these plants was basically one of the chelation and removal of ferrous ion (which take part in the photophily rhythms) from the plant (Oota, 1971).

6.4. RESIDUE

Pertinent data regarding dithiocarb residues in aquatic environments or organisms were not located in the available literature.

6.5. OTHER RELEVANT INFORMATION

The embryotoxic effects and teratogenicity of dithiocarb have been studied in embryos of the frog, Microhyla ornata. Based on mortality during the 72 hours subsequent to exposure, a 24-hour LC_{50} value of 3.0 mg/ℓ was reported (Ghate and Mulherkar, 1980). At concentrations between 1 and 3 mg dithiocarb/ℓ, embryos were severely malformed. Abnormalities included delayed growth, inhibition of pigment development, and abnormal notochord development with curvature of the body axis. At 0.5 mg/ℓ dithiocarb induced the development of abnormal, wavy notochords in exposed embryos.

Dithiocarb, acting as a chelating agent, has been found to remove the metals nickel, chromium and mercury from the gills, liver, kidney and brain of the fish, Notopterus notopterus (Verma et al., 1981). Initially the fish were exposed to metal salt solutions for 30 days, during which time the tissues accumulated metals. Subsequently, fish were exposed to 30.2 mg dithiocarb/ℓ for 7 days and examined for tissue-metal concentrations. Dithiocarb was most effective in removing nickel from the liver and gills (56.57 and 48.19% removed, respectively), with 14.78 and 17.91% chromium and 14.54 and 24.86% mercury removed from the liver and gills, respectively.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Information on existing guidelines and standards for human exposure to dithiocarb was not located in the available literature.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of dithiocarb were not located in the available literature.

8. RISK ASSESSMENT

Although IARC (1976) found the results of the carcinogenicity bioassay in two strains of mice (BRL, 1968; Innes et al., 1969) to be insufficient for assessing the carcinogenic potential of dithiocarb, a Fisher Exact test run by Syracuse Research Corporation indicates that the data for hepatoma incidence in treated male $B6C3F_1$ mice are statistically significantly different from controls. In the study (BRL, 1968; Innes et al., 1969), the mice were given 215 mg dithiocarb/kg daily by gavage from days 7-28 of age, after which dithiocarb was administered in the diet at a level of 692 ppm for 18 months. Assuming that a mouse consumes the equivalent of 13% of its body weight/day, the dose for the dietary portion of the study was 90.0 mg/kg/day. The TWA dose for the entire study period (dietary and gavage) was then calculated to be 95 mg/kg/day. Based on the hepatoma response of male $B6C3F_1$ (7/17 treated versus 8/79 control mice, P=0.00447) and using the linearized multistage model developed by Kenneth Crump and adopted by the U.S. EPA (1980), a carcinogenic potency factor (q_1^*) of 2.48×10^{-1} $(mg/kg/day)^{-1}$ can be derived for humans. The corresponding dose associated with an increased lifetime cancer risk of 10^{-5} is 4.03×10^{-5} mg/kg/day or 2.82×10^{-3} mg/day for a 70 kg man. Complete data for derivation of the q_1^* are presented in Appendix II.

However, the carcinogenicity data for dithiocarb were considered to be adequate evidence of carcinogenicity to animals by IARC (1976; 1982). Therefore, ADI will also be estimated for humans from the available chronic or subchronic toxicity data. In the NCI (1979) carcinogenicity study, 14/50 female rats receiving dithiocarb at a dietary level of 1250 ppm (62.5 mg/kg/day) developed cataracts, while no cataracts were observed in female control

rats. Since this was the lowest dose tested in the bioassay, it is impossible to define a NOAEL from this study. A subchronic study by Sunderman et al. (1967), however, tested dithiocarb at oral doses of 30 mg/kg/day with no effect in rats or dogs treated for 90 days. Although this latter study is only of subchronic duration, it represents a better choice as a basis for the development of an ADI when compared to the chronic bioassay because of a dose which caused no-effects was established. An ADI can be calculated from this subchronic study in the following manner:

$$\text{ADI} = 30 \text{ mg/kg/day} \times 70 \text{ kg} \div 1000.$$
$$= 2.1 \text{ mg/d}$$

For this calculation, it was assumed that the average person weighs 70 kg. The uncertainty factor of 1000 represents 10-fold each for both intra- and interspecies variability to the toxicity of dithiocarb in lieu of chemical specific data, and an additional 10-fold to extrapolate the results of subchronic to chronic exposures. An ADI based on the development of cataracts in female rats after 2 years of exposure (NCI, 1979), is higher than this latter value (62.5 mg/kg/d x 70 kg ÷ 1000 ~ 4.4 mg/d and leads some support to the overall calculation.

9. REFERENCES

Aaseth, J., N.E. Soeli and O. Foerre. 1979. Increased brain uptake of copper and zinc in mice caused by diethyldithiocarbamate. Acta Pharmacol. Toxicol. 45(1): 41-44.

Baselt, R.C. and V.W. Hanson. 1982. Efficacy of orally-administered chelating agents for nickel carbonyl toxicity in rats. Res. Commun. Chem. Pathol. Pharmacol. 38(1): 113-124.

Bluzat, R., O. Jonot and J. Seuge. 1982a. Acute toxicity of a fungicide, Thirame (Dithiocarbamate) in the fresh-water amphipodal crustacean, Gammarus pulex. Environ. Pollut. Ser. A-Ecological and Biological. 29(3): 225-233. (Fre.)

Bluzat, R., O. Jonot and J. Seuge. 1982b. Toxicite aigue d'un fongicide, le thirame (Dithiocarbamate), chez le mollusque pulmone d'eau donce Lymnaea stagnalis. Coll. Internat. d'Ecotoxicologie, INSERM Nov. 17-19, 1981. 59: 651 Villeneuve d'Ascq, France. (Cited in Bluzat et al., 1982a.)

Brink, R.H., Jr. 1976. Studies with chlorophenols, acrolein, dithiocarbamatale biodegradation units. Proc. 3rd Int. Biodeg. Sym. p. 785-791.

BRL (Bionetics Research Laboratories). 1968. Evaluation of carcinogenic, teratogenic and mutagenic activities of selected pesticides on industrial chemicals. Vol. 1. Carcinogenic Study Prepared for National Cancer Institute. U.S. Dept. Commerce, Nat'l. Tech. Info. Service, Washington, DC. NTIS PB-223159.

Brotherton, J. 1977. Assessment of spermicides by a stripping technique against human spermatozoa. J. Reprod. Fertil. 51(2): 383-391. Chem. Abstr. 88(17)115582a.

Burkart, P., H. Dautzenberg and H. Lang. 1968. Kinetic study of the decomposition of thiocarbamates. Faserforsch. Textiltech. (Ger.) 19(7): 325-332.

Ceruzzi, F. 1974. Action of sodium diethyldithiocarbamate on Bacillus subtilis and other microorganisms. Rev. Fac. Cienc. Med. Cordoba. 32(3-4): 313-319. Chem. Abstr. 84(17)116302p.

Collins, G.G.S. and G.B. West. 1968. Pharmacological actions of diethyl dithiocarbamate on rabbit and rat ileum. Br. J. Pharmacol. Chemother. 32(2): 403-409. Chem. Abstr. 68(15)67603w.

Craven, M.R., D.K. Luscombe and P.J. Nicholls. 1976. Absorption, elimination and duration of action of diethyldithiocarbamate in animals. J. Pharm. Pharmacol. 28(Suppl.): 38.

Crossley, H.L., J.J. Defeo and D.R. Defanti. 1969. Effect of sodium diethyl dithiocarbamate (DDC) on renal hypertension in rats. J. Pharm. Sci. 58(12): 1481-1484. Chem. Abstr. 72(9)41475p.

Danscher, G. and F.J. Fjerdingstad. 1975. Diethyldithiocarbamate (Antabuse). Decrease of brain heavy metal staining pattern and improved consolidation of shuttle box avoidance in goldfish. Brain Res. 83(1): 143-155.

Doggett, N.S. and P.S.J. Spencer. 1973. Pharmacological properties of centrally-administered agents which interfere with neurotransmitter function. Comparison with the central depressant effects of ouabain. Br. J. Pharmacol. 47(1): 26-38. Chem. Abstr. 78(25)154802k.

Edington, N. and J.M. Howell. 1966. Changes in the nervous system of rabbits following the administration of sodium diethyldithiocarbamate. Nature. 210: 1060-1062.

Edington, N. 1968. The effect of diethyldithiocarbamate on brain amine levels in the rabbit. J. Pharm. Pharmacol. 20(7): 577-578. Chem. Abstr. 69(13)50841v.

Gale, G.R., A.B. Smith and E.M. Walker, Jr. 1981. Diethyldithiocarbamate in treatment of acute cadium poisoning. Ann. Clin. Lab. Sci. 11(6): 476-483.

Ghate, H.V. and L. Mulherkar. 1980. Effect of sodium diethyldithiocarbamate on developing embryos of the frog, Microhyla ornata. Indian J. Exp. Biol. 18(9): 1040-1042. (Cited in U.S. EPA, 1983.)

Harman, D., H.J. Curtis and J. Tilley. 1970. Chromosomal aberrations in liver cells of mice fed free radical inhibitor. J. Gerontol. 25: 17-19.

Howell, J. McC. 1964. Effect of sodium diethyldithiocarbamate on blood copper levels and pregnancy in the rabbit. Nature. 201: 83-84.

Howell, J. McC., J. Ishmael, R. Ewbank and W.F. Blakemore. 1970. Changes in the central nervous system of lambs following the administration of sodium diethyldithiocarbamate. Acta Neuropathol. 15(3): 197-207. Chem. Abstr. 78(15)93307d.

IARC (International Agency for Research on Cancer). 1976. Sodium diethyl dithiocarbamate. In: Some Carbamates, Thiocarbamates and Carbazides. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. WHO, IARC, Lyon, France. 12: 217-223.

IARC (International Agency for Research on Cancer). 1982. Chemicals, Industrial Processes and Industries Associated with Cancer in Humans. IARC Monographs, Volumes 1 to 29. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyon, France. Monographs Supplement 4. p. 12 and 267.

Innes, J.R.M., B.M. Ulland, M.G. Valerio, et al. 1969. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. J. Natl. Cancer Inst. 42: 1101-1114.

Iwata, H., K. Watanabe, H. Miichi and Y. Matsui. 1970. Accumulation of copper in the central nervous system on prolonged administration of sodium diethyldithiocarbamate to rats. Pharmacol. Res. Commun. 2(3): 213-230. Chem. Abstr. 74(21)110135h.

Kaufman, D.D. 1967. Degradation of carbamate herbicides in soil. J. Agr. Food Chem. 15: 582-591.

Kihlman, B.A. 1957. Experimentally induced chromosome aberrations in plants. I. The production of chromosome aberrations by cyanide and other heavy metal complexing agents. J. Biophys. Biochem. Cytol. 3: 363-380.

Kleinrok, Z., I. Zebrowska-Lupina and M. Wielosz. 1970. Central effects of diethyldithiocarbamate administered intraventricularly in rats. Neuropharmacology. 9(5): 451-455. Chem. Abstr. 74(3)11805v.

Lopatecki, L.E. and W. Newton. 1952. The composition of dithiocarbamate fungicides with special reference to the volatile products. Can. J. Bot. 30: 131-138.

Maggiore, A., N. Savarese, M.G. Ficarra, F. Orecchio and F. Ghezzo. 1981. Biological effects of dithiocarbamates. Changes in serum leucine aminopeptidase activity in vitro caused by sodium diethyldithiocarbamate (NaODTC). Quad, Sclavo, Diagn. Clin. Lab. 17: 450-457. Chem. Abstr. 97:1872t.

Magos, L. and J.A. Jarvis, Ed. 1981. The paradox effect of carbon disulfide and diethyldithiocarbamate on adrenal dopamine-beta-hydroxylase. G. Ital. Med. Lav. 3(2-3): 107-108. Chem. Abstr. 96:1582k.

Maj, J. and J. Vetulani. 1970. Pharmacological properties of N,N-disubsti tuted dithiocarbamates and their effect on the brain catecholamine levels. Eur. J. Pharmacol. 9(2): 183-189. Chem. Abstr. 73(1)2390h.

NCI (National Cancer Institute). 1979. Bioassay of sodium diethyldithiocarbamate for possible carcinogenicity. NCI Carcinogenesis Tech. Rep. Ser. No. 172. p. 100. [Also published as DHEW (NIH) 79-1728.]

Neveu, P.J., N. Buscot and D. Thierry. 1980. Effect of sodium diethyl dithiocarbamate on mitogen induced lymphoproliferation in vitro. Biomed. Express. 33(8): 247-248.

NIOSH (National Institute for Occupational Safety and Health). 1983. RTECS (Registry of Toxic Effects of Chemical Substances). February, 1983.

Oota, Y. 1971. Disappearance of rhythmicity in growth response to dark and light-breaks in Lemna gibba G3 due to iron deficiency. Plant Cell Physiol. 12: 255-266.

Rasul, A.R. and J. McC. Howell. 1973. Response of the peripheral and central nervous system of the rabbit to sodium diethyldithiocarbamate. Acta Neuropathol. 24(2): 161-173.

Renoux, G. and M. Renoux. 1981. Immunologic activity of DTC: Potential for cancer therapy. Prog. Cancer Res. Therap. 16: 427-440.

Rice, E.W. 1964. Morphological changes in human spermatozoa following treatment of semen with certain dialkyldithiocarbamates. Exp. Cell Res. 34: 186-188.

Sakai, K., T. Tadano, K. Kisara and Y. Kimura. 1979. Effects of diethyl dithiocarbamate on ejaculatory inhibition and change monoamine levels of accessory glands. Nippon Yakurigaku Zasshi. 75(5): 425-432. (Japanese). Chem. Abstr. 91(25)204418f.

Sandmeyer, E.E. 1981. Organic Sulfur Compounds. In: G.D. Clayton and F.E. Clayton, Ed., Patty's Industrial Hygiene and Toxicology. 3rd rev. ed., Vol. 2A. John Wiley and Sons, Inc., NY. p. 2100.

SRI (Stanford Research Institute). 1983. Directory of Chemical Producers Stanford Res. Inst., Stanford, CA. p. 859.

Stromme, J.H. 1965. Metabolism of disulfiram and diethyldithiocarbamate in rats with demonstration of an in vivo ethanol-induced inhibition of the glucuronic acid conjugation of the thiol. Biochem. Pharmacol. 14: 393-410.

Sunderman, F.W., O.E. Paynter and R.B. George. 1967. Effects of the protracted administration of the chelating agent, sodium diethyldithiocarbamate (dithiocarb). Am. J. Med. Sci. 254(1): 46-56. Chem. Abstr. 67(15)72225h].

Tate, R.L. and M. Alexander. 1974. Formation of dimethylamine and diethylamine in soil treated with pesticides. Soil Sci. 118(5): 317-321.

U.S. EPA. 1980. Guidelines and Methodology for the Preparation of Health Effect Assessment Chapters of the Ambient Water Quality Documents. Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1977. TSCA Plant and Production Search System. Searched through CIS. Feb. 1983.

Vennerod, A.M. 1970. Effects of tetraethylthiuram disulfide (disulfiram), diethyldithiocarbamate and ethanol on factors of the kinin system in human blood. 28(6): 454-465. Chem. Abstr. 74(19)98020g.

Verma, S.R., M. Jain and R.C. Dalela. 1981. In vivo removal of a few heavy metals in certain tissues of the fish, Notopterus notopterus. Environ. Res. 26(2): 328-334.

Zemaitis, M.A. and F.E. Greene. 1979. In vivo and in vitro effects of thiuram disulfides and dithiocarbamates on hepatic microsomal drug metabolism in the rat. Toxicol. Appl. Pharmacol. 48(2): 343-350. Chem. Abstr. 91(11)84602n.

APPENDIX I

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
TSCAPP
AQUIRE
EPCASR
Chemical Industry Notes

Most of these searches were conducted in February, 1983; a few were conducted March-May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. TLVs: Documentation of the Threshold Limit Values. 4th ed. Supplemental Documents through 1981. Cincinnati, OH. p. 486.

ACGIH (American Conference of Governmental Industrial Hygienists). 1982. Documentation of the Threshold Limit Values for Chemical Substances in Work Air. Cincinnati, OH. p. 94.

Bruin, P., G.J. Bergen and J.J. Desta, Ed. 1980. Handling Chemicals Safely. 2nd ed. Dutch Assoc. of Safety Experts, Dutch Chemical Industry Assoc., and Dutch Safety Institute, The Netherlands. p. 1013.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology. 3rd rev. ed. Vol. 2A. John Wiley and Sons, NY. p. 2878.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology. 3rd rev. ed. Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology. 3rd rev. ed. Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology. 3rd ed. Publishing Sciences Group, Inc., MA. p. 575.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. p. 700.

Muir, G.D., Ed. 1977. Hazards in the Chemical Laboratory. 2nd ed. The London Chemical Society, London. p. 473.

NTP (National Toxicology Program). 1982. Carcinogenesis Testing Program. Chemicals on Standard Protocol. Management Status. Report date: December 31, 1982.

Proctor, N.H. and J. P. Hughes. 1978. Chemical Hazards of the Work-place. J.B. Lippincott Co., Philadelphia. p. 533.

Sax, I.N. 1979. Dangerous Properties of Industrial Materials. 5th ed. Van Nos Reinhold Co., NY.

APPENDIX II
CANCER DATA SHEET FOR DERIVATION OF q_1^*

Compound:	Sodium Diethyldithiocarbamate
Reference:	BRL, 1968; Innes et al., 1969
Species, Strain, Sex:	Mice, $B6C3F_1$, males
Body Weight:	0.043 kg (measured)
Length of Exposure (ℓe)	= 546 days
Length of Experiment (Le)	= 546 days
Lifespan of Animal (L)	= 730 days (assumed)
Tumor Site and Type:	liver, hepatoma
Route, Vehicle:	Oral, by gavage in distilled water for 21 days, then in diet for 525 days

Experimental Doses or Exposures	Transformed Dose mg/kg/day	Incidence No. Responding/ No. Tested (or Examined)
0	0	8/79
215 mg/kg/day x 21 days, then 692 ppm in diet x 525 days	95	7/17

Human $q_1^* = 2.48 \times 10^{-1}$ $(mg/kg/day)^{-1}$

10^{-5} risk level = 4.03×10^{-5} mg/kg/day = 2.82×10^{-3} mg/day for 70 kg man